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10/594,266	03/21/2007	Masakazu Ichinose	66314(46342)	5665

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EXAMINER	
LEE, JAE W	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/594,266	ICHINOSE ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *1-14 and 19-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09/26/2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *09/26/2006; 01/16/2007; 10/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

Claims 1-41 are pending in this application.

Priority

The instant application is the 371 national stage entry of PCT/JP05/06444, filed on 03/25/2005. The Examiner notes that the requirements of national stage entry of the instant application had been completed (note assigned U.S. filing date) within 30 months of the earliest claimed priority date; the related international application includes both a search report and a preliminary examination report. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to a foreign patent application JAPAN 2004-092064 filed without English translation on 03/26/2004.

Election

Applicant's election of Group V, Claims 15-18, and SEQ ID NO: 2 in the reply filed on 10/20/2009, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). It is also noted by the Examiner that the restriction/election requirement between SEQ ID NOs was NOT a species election (see previous office action mailed on 07/22/2009).

Claims 1-14 and 19-41, and SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60 and SEQ ID NO: 62 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Specification

The " BRIEF DESCRIPTION OF THE DRAWINGS" for Figure 7 is objected to because its description of Figure 7 is incomplete. On page 12, lines 19-22, Figure 7 is described as a single figure (graph), when in fact, Figure 7 contains two separate figures (graphs). The Examiner suggests that Applicants amend this section to properly describe both of the graphs shown in Figure 7.

The use of the trademarks "Affymetrix", have been noted in this application (See page 86, lines 4-5). Although the use of trademarks is permissible in patent

applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks. The Examiner suggests capitalizing each letter of the word or including a proper trademark symbol, such as ™ or © following the word.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, Applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly page 16, lines 8-9, and page 45, line 22 of the specification containing amino acid sequences, and therefore, they should be represented by a proper sequence identifier number.

Appropriate correction is required.

Claim Objections

Claims 15-18 are objected to because of the following informalities:

Claims 15 and 17 are objected to for containing recitations of non-elected subject matter, i.e., "SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10, SEQ ID NO: 12, SEQ ID NO: 14, SEQ ID NO: 16, SEQ ID NO: 18, SEQ ID NO: 20, SEQ ID NO: 22, SEQ ID NO: 24, SEQ ID NO: 26, SEQ ID NO: 28, SEQ ID NO: 30, SEQ ID NO: 32, SEQ ID NO: 34, SEQ ID NO: 36, SEQ ID NO: 38, SEQ ID NO: 40, SEQ ID NO: 42, SEQ ID NO: 44, SEQ ID NO: 46, SEQ ID NO: 48, SEQ ID NO: 50, SEQ ID NO: 52, SEQ ID NO: 54, SEQ ID NO: 56, SEQ ID NO: 58, SEQ ID NO: 60 or SEQ ID NO: 62". The Examiner suggests deletion of the noted phrase.

Claims 15-18 are objected to for the recitation of "represented by" which can be substantially improved with respect to form. The Examiner suggests replacing the noted phrase with ---of---. In the interest of advancing prosecution, the noted phrase is interpreted as suggested by the Examiner.

Claim 17 is objected to because the recitation of "bySEQ" in line 3 can be substantially improved with respect to form. The Examiner suggests inserting a space between "by" and "SEQ". In the interest of advancing prosecution, the noted phrase is interpreted as suggested by the Examiner.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-18 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 15 and 17 (16 and 18 dependent therefrom) recite the phrase "substantially the same amino acid sequence" which is unclear and indefinite. It is unclear since "substantially the same amino acid sequence" can vary widely depending on the person making the determination as to what degree of similarity is regarded as being "substantially the same amino acid sequence". For instance, one may interpret the phrase as any amino acid sequence with 50% sequence identity to a reference sequence, while another may interpret the phrase as any amino acid sequence with 95% sequence identity to a reference sequence. As such, metes and bounds of the noted phrase are unclear and indefinite. It is noted by the Examiner that the noted phrase is not defined in the specification. In the interest of advancing prosecution, the phrase “the same or substantially the same amino acid sequence as the amino acid sequence represented by SEQ ID NO: 2” is interpreted as "the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2 or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2".

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are directed to a genus of [1] methods of screening a prophylactic/therapeutic agent for respiratory diseases, which comprises using a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof; and [2] kits for screening a prophylactic/therapeutic agent for respiratory diseases, comprising a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof (italicized for added emphasis). See above Claims objections and the rejection under 35 U.S.C. 112 2nd paragraph for the claim interpretation.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of [compositions or methods], it must be clear that: (1) the identifying

characteristics of the claimed [compositions or methods] have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these (paraphrased from Enzo Biochemical Inc. v. Gen-Probe Inc. (CAFC (2002) 63 USPQ2d 1609).

University of Rochester v. G.D. Searle & Co. (69 USPQ2d 1886 (2004)) specifically points to the applicability of both Lily and Enzo Biochemical to methods of using products, wherein said products lack adequate written description. While in

University of Rochester v. G.D. Searle & Co. the methods were held to lack written description because not a single example of the product used in the claimed methods was described, the same analysis applies wherein the product, used in the claimed methods, must have adequate written description as noted from Enzo Biochemical (see above).

The specification discloses a method of screening a therapeutic agent comprising using cholesterol 25-hydroxylase comprising the amino acid sequence as set forth in SEQ ID NO: 2 (see Example 8 on pages 97-98 of the specification). However, the disclosure fails to provide adequate written description for [1] a method of screening a prophylactic/therapeutic agent for respiratory diseases, which comprises using a genus of proteins comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof; and [2] a kit for screening a prophylactic/therapeutic agent for respiratory diseases, comprising a genus of proteins comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof (italicized for added emphasis, see above Claims objections and the rejection under 35 U.S.C. 112 2nd paragraph for the claim interpretation).

As such, one of skill in the art would not have recognized that Applicants were in possession of the genus of inventions as claimed since: [I] a genus of proteins

comprising any partial peptide, i.e., any fragment, of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide as recited in claims encompasses widely variant proteins/peptides, which may or may not have the desired biological function/activity, i.e., having a biological activity which is useful in screening of a prophylactic/therapeutic agent for respiratory diseases; [II] the disclosure of the specification is limited to a method of screening a therapeutic agent comprising using cholesterol 25-hydroxylase comprising the amino acid sequence as set forth in SEQ ID NO: 2 (see Example 8 on pages 97-98 of the specification); [III] the disclosure of the specification lacks correlation between structure-to-function, i.e., how the genus of proteins/peptides comprising [i] any partial peptide of the amino acid sequence of SEQ ID NO: 2, or [ii] any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide correlate to a desired biological function/activity, which is useful in screening of a prophylactic/therapeutic agent for respiratory diseases; and [IV] it is highly unpredictable for a skilled artisan to predict (1) a function of a protein/peptide based on its primary structure, i.e., the amino acid sequence, and (2) a structure of a protein/peptide based on its biological function/activity. In support of this notion, proteins having very different structures can have the same function (Kisselev et al, 2002), while proteins having very similar structure can have different activities (Witkowski et al, 1999; Wishart et al, 1995).

In this case, the specification fails to describe any identification of structural characteristics or properties of the genus of proteins comprising [i] any partial peptide of

the amino acid sequence of SEQ ID NO: 2, or [ii] any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, so that a skilled artisan can envision those proteins/peptides having a desired biological activity that are capable of being used in screening of a prophylactic/therapeutic agent for respiratory diseases from those that are not capable. Taken together, a method of using the genus of "proteins" or a kit comprising said genus of "proteins" as described above encompasses widely variant structures which may or may not have the desired biological function, and given the lack of additional representative species of said genus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for a method of screening a therapeutic agent for airway inflammation comprising using cholesterol 25-hydroxylase having the amino acid sequence as set forth in SEQ ID NO: 2, or a kit for screening a therapeutic agent for airway inflammation comprising cholesterol 25-hydroxylase having the amino acid sequence as set forth in SEQ ID NO: 2 (see Example 8 on pages 97-98 of the specification), does not

reasonably provide enablement for [1] a method of screening a prophylactic/therapeutic agent for respiratory diseases, which comprises using a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2, its partial peptide*, or a salt thereof; and [2] a kit for screening a prophylactic/therapeutic agent for respiratory diseases, comprising a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2, its partial peptide*, or a salt thereof (italicized for added emphasis). See above Claims objections and the rejection under 35 U.S.C. 112 2nd paragraph for the claim interpretation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2nd 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach

how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breath of the claims. Claims 15-18 are so broad as to encompass [1] a method of screening a *prophylactic*/therapeutic agent for respiratory diseases, which comprises using a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof to screen a *prophylactic*/therapeutic agent capable of *preventing respiratory diseases*; and [2] a kit for screening a *prophylactic*/therapeutic agent for respiratory diseases including screening an agent capable of *preventing respiratory diseases*, comprising a protein comprising [i] the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, *its partial peptide*, or a salt thereof, or [ii] *any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2*, *its partial peptide*, or a salt thereof (italicized for added emphasis). See above Claims objections and the rejection under 35 U.S.C. 112 2nd paragraph for the claim interpretation. The enablement provided is not commensurate in scope with the claim due to the extremely large number of proteins of unknown structure that are used by the recited methods and comprised by the recited kits. Furthermore, with regard to the recitation of "*prophylactic*" agent in claims 15-18, it is noted by the Examiner that the specification does not enable one of skill in the art to screen a “prophylactic" agent for respiratory diseases since the phrase “prophylactic agent” is interpreted as an agent which prevents respiratory diseases. There is nothing

in the specification which demonstrates that an identified agent, using the method or the kit as claimed, produces the effect of prophylaxis or prevention of respiratory diseases. The Examiner suggests deletion of "prophylactic/" in claims 15 and 17.

In the instant case, the specification enables a single species, i.e., a method of screening a therapeutic agent for airway inflammation comprising using cholesterol 25-hydroxylase having the amino acid sequence as set forth in SEQ ID NO: 2, or a kit for screening a therapeutic agent for airway inflammation comprising cholesterol 25-hydroxylase having the amino acid sequence as set forth in SEQ ID NO: 2 (see Examples 7-8 on pages 96-98 of the specification).

The amount of direction or guidance presented and the existence of working examples. The specification discloses a method of screening a therapeutic agent for airway inflammation comprising using cholesterol 25-hydroxylase having the amino acid sequence as set forth in SEQ ID NO: 2 (see Examples 7-8 on pages 96-98 of the specification). However, the specification fails to provide any clue as to the structural elements required in any proteins comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, which exhibits a desired biological function/activity so that one skilled in the art can use such proteins/peptides as intended by Applicants, i.e., in a method or a kit for screening a prophylactic/therapeutic agent which is capable of preventing respiratory diseases. No correlation between structure and function has been presented. There is no information or guidance as to which amino acid residues in the polypeptide of SEQ ID NO: 2 can be

modified and which ones are to be conserved to create any proteins comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, displaying the same biologically function/activity as that of the polypeptide of SEQ ID NO: 2 so that such proteins/peptides can be used in a method of screening a prophylactic/therapeutic agent capable of preventing respiratory diseases.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses a human cholesterol 25-hydroxylase which is identical to Applicants' SEQ ID NO: 2, neither the specification nor the art provides a correlation between structure and such function/activity such that one of skill in the art can envision the structure of any proteins comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, which display the same biologically function/activity as that of the polypeptide of SEQ ID NO: 2 so that such proteins/peptides can be used in a method or a kit for screening a prophylactic/therapeutic agent for respiratory diseases. In addition, the art does not provide any teaching or guidance as to (1) which changes can be made to the polypeptide of SEQ ID NO: 2 such that the resulting variant polypeptide, including any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, would display a desired biological

function/activity, i.e., capable of being used in a method of screening a prophylactic/therapeutic agent for respiratory diseases, optionally wherein said prophylactic agent is capable of preventing respiratory diseases, or (2) the general tolerance of the human cholesterol 25-hydroxylase comprising the amino acid sequence as set forth in SEQ ID NO: 2 to structural modifications and the extent of such tolerance. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. In support of this notion, proteins having very different structures can have the same function (Kisselev et al, 2002), while proteins having very similar structure can have different activities (Witkowski et al, 1999; Wishart et al, 1995).

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or

isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process, all possible proteins/peptides comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, for those that display a desired biologically function/activity found in the polypeptide of SEQ ID NO: 2 so that such protein/peptides can be used in a method or a kit for screening a prophylactic/therapeutic agent for respiratory diseases. In the absence of (1) a rational and predictable scheme for modifying any residue in the proteins comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide, which would maintain the desired biological function/activity, i.e., display a desired biologically function/activity found in the polypeptide of SEQ ID NO: 2 so that such proteins/peptides can be used in a method of screening a prophylactic/therapeutic agent for respiratory diseases, and/or (2) a correlation between structure and the desired biological function/activity, one of skill in the art would have to test an essentially infinite number of proteins comprising any partial peptide of the amino acid sequence of SEQ ID NO: 2, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2 or its partial peptide to determine which ones have a desired biological function that is useful in a method or a kit for screening a prophylactic/therapeutic agent for respiratory diseases, optionally wherein said prophylactic agent is capable of preventing respiratory diseases.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to make and use the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15-18 are rejected under 35 U.S.C. § 102(b) as being anticipated by Russell et al. (Cholesterol 25-Hydroxylase, WO 2000/23596, published on 04/27/2000, see IDS).

The instant claims are drawn to [1] a method of screening a prophylactic/therapeutic agent for respiratory diseases, which comprises using a protein comprising the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, its partial peptide, or a salt thereof, or any amino acid sequence having 50%

sequence identity with the amino acid sequence of SEQ ID NO: 2, its partial peptide, or a salt thereof; and [2] a kit for screening a prophylactic/therapeutic agent for respiratory diseases, comprising a protein comprising the same amino acid sequence as the amino acid sequence of SEQ ID NO: 2, its partial peptide, or a salt thereof, or any amino acid sequence having 50% sequence identity with the amino acid sequence of SEQ ID NO: 2, its partial peptide, or a salt thereof. See above Claims objections and the rejection under 35 U.S.C. 112 2nd paragraph for the claim interpretation.

It is noted by the Examiner that the recitation of "for respiratory diseases", in the preamble of Claims 15 and 17, has not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See *In re Hirao*, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and *Kropa v. Robie*, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

The reference of Russell et al. specifically teaches a method of screening for an agent that modulates the interaction of human cholesterol 25-hydroxylase polypeptide as set forth in SEQ ID NO: 2 (which is identical to Applicant's SEQ ID NO: 2, see below sequence alignment from SCORE 20091211_121822_us-10-594-266-2.rag), to a binding target, said method comprising the steps of: incubating a mixture comprising said polypeptide, a binding target of said polypeptide, and a candidate agent; detecting the binding affinity of said polypeptide to said binding target to determine an agent-

biased affinity, wherein a difference between the agent-biased affinity and the reference affinity indicates that said agent modulates the binding of said polypeptide to said binding target, which meets the limitation of claims 15 and 16 (see page 23 under "Inhibitor studies", pages 29 and 37, and pages 2-3 of the sequence listing of Russell et al.). Russell et al. further teach transformation of cells, i.e., DH10B cells or CHOP cells, on 6-well plates with cDNA of human cholesterol 25-hydroxylase polypeptide, wherein the human cholesterol 25-hydroxylase polypeptides are expressed in the cells for use in the activity-based screening method as mentioned above, which meet the limitations of claims 17 and 18. Therefore, teachings of Russell et al. anticipate claims 15-18.

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  Query Match             100.0%;  Score 1535;  DB 1;  Length 272;
  Best Local Similarity   100.0%;
  Matches  272;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MSCHNCSDPQVLCSSGQLFLQPLWDHLRSWEALLQSPFFPVIFSITTYVGFCLPFVVLDI 60
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MSCHNCSDPQVLCSSGQLFLQPLWDHLRSWEALLQSPFFPVIFSITTYVGFCLPFVVLDI 60

Qy         61 LCSWVPALRRYKIHPDFSPSAQQLLPCLGQTLYQHVMFVFPVTLLHWARSPALLPHEAPE 120
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Qy        121 LLLLLHHILFCLLLFDMEFFVWHLLHHKVPWLYRTFHKVHHQNSSSFALATQYMSVWELF 180
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Qy        181 SLGFFDMMNVTLLGCHPLTTLTFHVVNIWLSVEDHSGYNFPWSTHRLVPFGWYGGVVHHD 240
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Qy        241 LHHSHFNCNFAPYFTHWDKILGTLRTASVPAR 272
              ||||||||||||||||||||||||||||||||
Db        241 LHHSHFNCNFAPYFTHWDKILGTLRTASVPAR 272
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Conclusion

Claims 15-18 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on M-F between 9:00-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE/
Examiner, Art Unit 1656